

## BRIEF COMMUNICATION

# Is disorganized schizophrenia a predictor of treatment resistance? Evidence from an observational study

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**Objective:** To investigate whether inpatients with disorganized schizophrenia are more resistant to treatment.

**Method:** Eighty-five inpatients were assessed at admission and at discharge for schizophrenia subtype, symptom severity, and treatment resistance criteria.

**Results:** Disorganized patients were significantly more treatment-resistant than paranoid patients (60%,  $p = 0.001$ ), and presented worse scores on the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression Scale (CGI-S), and the Global Assessment of Functioning Scale (GAF) ( $p < 0.001$ ). Although the difference was not significant, 80% of treatment-resistant patients with disorganized schizophrenia responded to clozapine.

**Conclusion:** Patients with the disorganized subtype of schizophrenia should benefit from clozapine as a second-line agent.

**Keywords:** Clozapine response; disorganized schizophrenia; treatment-resistant schizophrenia; subtypes of schizophrenia; clinical predictors

## Introduction

The subtypes of schizophrenia were removed from the DSM-5.<sup>1</sup> The justification of the joint committee was that these subtypes have shown poor reliability and stability, and have not supported specific treatment. As an alternative, a continuum of blended psychopathological dimensions has been proposed to explain clinical heterogeneity.<sup>1</sup>

In 1881, Hecker described an entity of early onset, typically during adolescence, characterized by the emergence of mood symptoms before the onset of psychotic and disorganized symptoms, progressing quickly to severe functional impairment and cognitive deterioration. He termed this entity “hebephrenia.” The features of hebephrenia prepared the ground for Kraepelin’s concept of *dementia praecox* and Bleuler’s “group of schizophrenias.”<sup>2</sup> Hebephrenia was also the base for the disorganized subtype criteria operationalized in the DSM-IV, where it had to satisfy the basic diagnostic criteria for schizophrenia and show prominence of at least two out of the following symptoms: disorganized speech, disorganized behavior, and flat or inappropriate affect.<sup>3</sup>

Few studies have addressed the prognosis of the disorganized subtype of schizophrenia, and patients with

this subtype seem to respond relatively poorly to treatment and have a worse long-term prognosis.<sup>4,5</sup> Although the use of subtypes has declined over time,<sup>6</sup> a recent study of 8,028 patients showed that disorganized schizophrenia and delusional disorder had good validity.<sup>7</sup>

Approximately 30% of patients will be treatment-resistant (TR) to antipsychotics. On the basis of several lines of evidence, there is a consensus that clozapine is the best antipsychotic for TR patients.<sup>8</sup>

This study aims to ascertain whether patients with disorganized schizophrenia (DS) are more TR than those with paranoid schizophrenia (PS), and whether prominence of disorganized symptoms is a predictor of treatment resistance. Only these subtypes were chosen because they have shown higher homogeneity and validity.<sup>7</sup>

## Methods

### Subjects

This was an observational study ( $n=85$ ), with data collected from consecutive admissions to the inpatient unit of Hospital das Clínicas Luzia de Pinho Melo (Mogi das Cruzes, state of São Paulo, Brazil), which is the referral hospital for psychiatric admissions in the area where the study was conducted, between 2011 and 2013. The inclusion criteria were: 1) presence of PS or DS as defined by the DSM-IV; 2) a lack of demonstrable organic brain disease (on computed tomography) or severe

mental retardation before onset; and 3) age between 12 and 60 years. Other subtypes were excluded, except for undifferentiated schizophrenia; patients with this subtype were allocated to the paranoid group or the disorganized group as seen fit. The study was approved by the local Ethics Committee, and all subjects and relatives provided written informed consent.

#### Diagnostic and symptoms assessment

All patients were administered the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning (GAF) scale, and the Clinical Global Impression - Severity (CGI-S) scale at baseline. PANSS and CGI-S were rated again after any switch in antipsychotic and at discharge. Diagnostic evaluation was performed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). To ensure accurate differentiation of the subtypes, the classification into DS or PS followed the hierarchical criterion of the SCID-I based on prominence of psychotic symptoms of module B. Patients presenting prominence of items B1 to B9 (delusion and hallucinations) were classified as PS, and those presenting prominence of items B11 to B13 (grossly disorganized behavior, grossly inappropriate affect, and disorganized speech) were classified as DS. Each psychopathological dimension score was calculated as the sum of the three most correlated items of the PANSS: 1) positive dimension = P1 + P3 + P6 (delusions, hallucinatory behavior, suspicious); 2) disorganized dimension = P2 + G10 + G11 (conceptual disorganization, disorientation, poor attention); 3) negative dimension = N1 + N2 + N3 (blunted affect, emotional withdrawal, poor rapport).

#### Antipsychotic treatment and TR criteria

Response was defined as a reduction of more than 40% in the baseline total PANSS score (subtracting the 30 initial points).<sup>9</sup> Treatment resistance was defined as an absence of response to two trials of antipsychotic (haloperidol, olanzapine, risperidone, or quetiapine). In this case, clozapine or combination therapy was introduced. The switch to a new antipsychotic occurred in three situations: 1) absence of response after 4 weeks on

any antipsychotic; 2) absence of response after 2 weeks on a previously trialed drug (full adherence before hospitalization reported by relatives); or 3) intolerance to side effects. All patients were rated by the first author, who was not blind to the subtype or to the choice of first medication.

#### Statistical analysis

The percentages of treatment resistance and response to clozapine, mean scores on the PANSS, CGI-S, and GAF scales, and socio-demographic data were compared between the DS and PS groups. The mean scores of the three psychopathological dimensions, age of onset, and duration of illness were controlled for treatment resistance. Statistical analyses were performed with SPSS version 17.0. Bivariate statistical analyses were performed using the most adequate statistical test for each situation (Fisher's exact test or Student's *t*-test for unequal variances). A *p*-value of < 0.05 was considered significant.

#### Results

Eight patients (9%) were excluded from the study, whereof three were subtyped as catatonic and five as residual. Only three of them were TR. The remaining sample comprised 25 (29.5%) patients with DS and 60 (70.5%) with PS. No differences were observed between the groups with respect to sex, age at hospitalization, and duration of illness. On the other hand, patients in the DS group were significantly more TR than those in the PS group, presented worse scores in the PANSS, CGI-S, and GAF (*p* < 0.01), and were younger at onset. After controlling for all TR patients, no such difference was found for earlier age of onset (*p* = 0.11) or duration of illness (*p* = 0.28). With respect to symptom dimensions, only the disorganized dimension (*p* = 0.004) was higher in the TR subgroup.

Clinical and demographic data are presented in Table 1.

#### Discussion

To the best of our knowledge, this was the first study to compare treatment resistance between two subtypes of

**Table 1** Clinical and demographic data comparing disorganized with paranoid subtype

Clinical and demographic variables	Disorganized	Paranoid	<i>p</i> -value
Number of patients (%)	25 (29.5%)	60 (70.5%)	-
TR (%)	15 (60%)	12 (20%)	0.001
PANSS (mean ± SD)	145.2 ± 16.0	126.3 ± 16.7	< 0.001
CGI-S (mean ± SD)	6.6 ± 0.49	5.8 ± 0.61	< 0.001
GAF (mean ± SD)	12.2 ± 6.6	24.1 ± 7.4	< 0.001
Gender, male (%)	14 (56.0%)	34 (56.7%)	1.00
Age, years (mean ± SD)	32.1 ± 11.7	33.0 ± 12.1	0.54
Age at onset, years (mean ± SD)	19.1 ± 6.0	24.5 ± 9.2	0.01
DI, years (mean ± SD)	12.8 ± 10.1	9.4 ± 9.3	0.15
Response to clozapine in TR group (%)	12 (80.0%)	8 (66.3%)	0.66

CGI-S = Clinical Global Impression Scale; DI = duration of illness; GAF = Global Assessment of Functioning Scale; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; TR = treatment-resistant.

schizophrenia using quantitative rating scales in an observational setting. While previous studies have not identified unequivocal clinical predictors of antipsychotic response, with regards to non-response, there is consistent evidence for the duration of untreated psychosis, poor premorbid function, and severity of the negative and cognitive/disorganized symptom dimensions as predictors.<sup>10,11</sup> In our results, the nonsignificant longer duration of illness and earlier age of onset among refractory patients would possibly be significant in a larger sample. On the other hand, disorganization was significantly predictive of treatment resistance even in a dimensional approach.

The observation that 80% of refractory DS responded to clozapine highlights the effectiveness of this medication in such patients. However, the literature on response to clozapine in patients with disorganization remains unclear. Joffe et al.<sup>12</sup> conducted a retrospective study of outpatients treated with clozapine, and those with the disorganized subtype showed greater clinical ( $p = 0.032$ ) and social ( $p = 0.024$ ) improvements than non-disorganized patients. In a recent study designed to investigate trends in clozapine prescription, Nielsen et al.<sup>13</sup> found higher prescription rates of clozapine for patients with DS. The percentage of disorganized patients taking clozapine was 29.7%, while only 11.3% of those with PS were on the drug ( $p < 0.001$ ). On the other hand, Rodriguez et al.,<sup>14</sup> found disorganization to be associated with non-response and partial response.

This study is limited by the small sample and the expectation bias of the rater. However, the observational follow-up design has the advantage of providing a picture consistent with clinical practice. Taking into account these preliminary results added to the reports listed above, the authors propose the use of clozapine as a second-line agent in DS. Definition of more reliable categorical subtypes is desirable, since the current opinion in DSM-5 regards only the dimensional view.

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### Disclosure

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